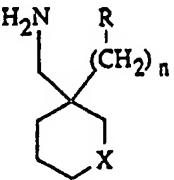
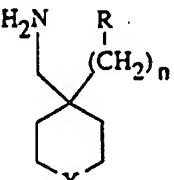




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/26, A61K 31/445, C07D 211/34, C07F 9/38, A61K 31/66, C07D 413/06, 401/06, 417/06, 419/06, 309/04, A61K 31/35, 31/41, C07D 407/06, 335/02, A61K 31/38		A1	(11) International Publication Number: WO 99/31057 (43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: PCT/US98/23991 (22) International Filing Date: 10 November 1998 (10.11.98)		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.	
(30) Priority Data: 60/069,773 16 December 1997 (16.12.97) US 60/104,904 20 October 1998 (20.10.98) US		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors; and (75) Inventors/Applicants (for US only): BRYANS, Justin, Stephen [GB/GB]; Dean Cottage, 3 W. Wickham Road, Balsham CB1 6DZ (GB). HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge, CB2 6SZ (GB). KNEEN, Clare, Octavia [GB/GB]; Slade Cottage, Petts LN, Little Walden, Essex CB10 1XH (GB). WUSTROW, David, Juergen [US/US]; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).			
(54) Title: 4(3)SUBSTITUTED-4(3)-AMINOMETHYL-(THIO)PYRAN OR -PIPERIDINE DERIVATIVES (=GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS			
 1D		 1E	
(57) Abstract Novel amines of formulas (1D) and (1E), or a pharmaceutically acceptable salt thereof, wherein: n is an integer of from 0 to 2; R is sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid, or hydroxamic acid; and X is -O-, -S-, -S(O)-, -S(O)2-, or NR'; wherein R' is hydrogen, straight or branched alkyl of from 1 to 6 carbons, or benzyl, -C(O)R'2 wherein R'2 is straight or branched alkyl of 1 to 6 carbons, benzyl or phenyl or -CO2R'3 wherein R'3 is straight or branched alkyl of from 1 to 6 carbons, or benzyl wherein the benzyl or phenyl groups can be unsubstituted or substituted by from 1 to 3 substituents selected from halogen, trifluoromethyl, and nitro, are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially IBS.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

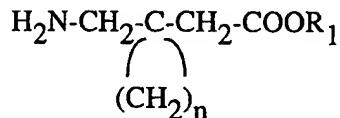
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

-1-

4(3)SUBSTITUTED-4(3)-AMINOMETHYL-(THIO)PYRAN OR -PIPERIDINE DERIVATIVES (=GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS

BACKGROUND OF THE INVENTION

Compounds of formula



5 wherein R₁ is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in
 United States Patent Number 4,024,175 and its divisional United States Patent
 Number 4,087,544. The uses disclosed are: protective effect against cramp
 induced by thiosemicarbazide; protective action against cardiazole cramp; the
 cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas;
 10 and improvement in cerebral functions. The compounds are useful in geriatric
 patients. The patents are hereby incorporated by reference.

Compounds of formula



wherein R₁ is a straight or branched alkyl group having from 1 to 6 carbon atoms,
 phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R₂ is hydrogen or methyl;
 20 and R₃ is hydrogen, methyl, or carboxyl are known in United States Patent
 Number 5,563,175 and various divisionals. These patents are hereby incorporated
 by reference. (See Suman-Chaulan N., et al., European Journal of Pharmacology,
 1993;244:293-301.)

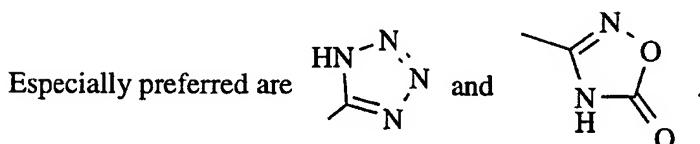
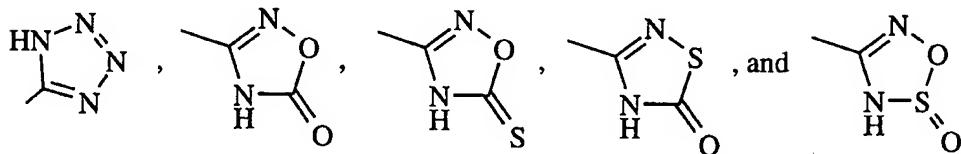
SUMMARY OF THE INVENTION

The compounds of the instant invention are novel amines and their pharmaceutically acceptable salts useful in a variety of disorders. The disorders include: epilepsy, faintness attacks, hypokinesia, cranial disorders, 5 neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammation, and gastrointestinal disorders such as irritable bowel syndrome.

The compounds of the invention are those of formulas 1D and 1E below. Preferred compounds are those of formulas 1D and 1E wherein R is a 10 sulfonamide selected from $-\text{NHSO}_2\text{R}_{15}$ or $-\text{SO}_2\text{NHR}_{15}$ wherein R_{15} is straight or branched alkyl or trifluoromethyl.

Other preferred compounds are those of formulas 1D and 1E wherein R is a phosphonic acid, $-\text{PO}_3\text{H}_2$.

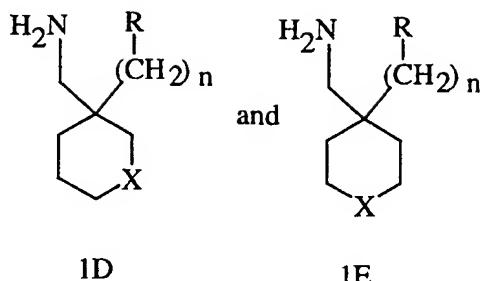
Other preferred compounds are those of formulas 1D and 1E wherein R is 15 selected from:



DETAILED DESCRIPTION OF THE INVENTION

20 The amines of the instant invention are compounds of formula 1D and 1E and the pharmaceutically acceptable salts thereof.

The compounds of the invention are those of formula



or a pharmaceutically acceptable salt thereof wherein:

n is an integer of from 0 to 2:

R is sulfonamide.

5 amide.

phosphonic acid.

heterocycle.

sulfonic acid

hydroxamic acid

$$\mathbf{S} = \mathbf{S}(0) \cup \mathbf{S}(0)$$

15 R'_1 is $\text{C}_1\text{H}_2\text{O}$, $\text{C}_1\text{H}_2\text{O}_2$, $\text{C}_1\text{H}_2\text{O}_3$, or NHR'_1 wherein R'_1 is hydrogen, straight or branched alkyl of from 1 to 6 carbons, benzyl, $-\text{C}(\text{O})\text{R}'_2$ wherein R'_2 is straight or branched alkyl of 1 to 6 carbons, benzyl or phenyl or $-\text{CO}_2\text{R}'_3$ wherein R'_3 is straight or branched alkyl of from 1 to 6 carbons, or benzyl wherein the benzyl or phenyl groups can be unsubstituted or substituted by from 1 to 3 substituents selected from halogen, trifluoromethyl, and nitro.

The following are specific compounds of the instant invention:

N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-methanesulfonamide;

(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-phosphonic acid;

20 2-(4-Aminomethyl-tetrahydro-pyran-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-

one;

3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-

25 C-[4-(1H-Tetrazol-5-ylmethyl)-tetrahydro-pyran-4-yl]-methylamine;

**N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-C,C,C-trifluoro-
nesulfonamide:**

3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[4-(2-Oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-tetrahydro-pyran-4-yl]-methylamine;

5 (4-Aminomethyl-tetrahydro-pyran-4-yl)-methanesulfonamide;

(4-Aminomethyl-tetrahydro-pyran-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-acetamide;

N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-

10 methanesulfonamide;

(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-tetrahydro-thiopyran-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

15 3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[4-(1H-Tetrazol-5-ylmethyl)-tetrahydro-thiopyran-4-yl]-methylamine;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

20 3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[4-(2-Oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-tetrahydro-thiopyran-4-yl]-methylamine;

(4-Aminomethyl-tetrahydro-thiopyran-4-yl)-methanesulfonamide;

25 (4-Aminomethyl-tetrahydro-thiopyran-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-acetamide;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-1-oxo-hexahydro-1λ⁴-thiopyran-4-ylmethyl)-

methanesulfonamide;

30 (4-Aminomethyl-1-oxo-hexahydro-1λ⁴-thiopyran-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

5 3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

10 C-[1-Oxo-4-(1H-tetrazol-5-ylmethyl)-hexahydro-1 λ ⁴-thiopyran-4-yl]-methylamine;

15 N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

20 3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

25 C-[1-Oxo-4-(2-oxo-2,3-dihydro-2 λ ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-hexahydro-1 λ ⁴-thiopyran-4-yl]-methylamine;

30 4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-methanesulfonamide;

(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-acetamide;

N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-ylmethyl)-methanesulfonamide;

25 (4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-yl)-N-hydroxy-acetamide;

30 3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-thione;

5 C-[1,1-Dioxo-4-(1H-tetrazol-5-ylmethyl)-hexahydro-1 λ^6 -thiopyran-4-yl]-methylamine;

10 N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

15 3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

20 C-[1,1-Dioxo-4-(2-oxo-2,3-dihydro-2 λ^4 -[1,2,3,5]oxathiadiazol-4-ylmethyl)-hexahydro-1 λ^6 -thiopyran-4-yl]-methylamine;

25 (4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-methanesulfonamide;

30 (4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-methanesulfonic acid;

35 N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-ylmethyl)-acetamide;

40 N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-ylmethyl)-2-phenyl-acetamide;

45 N-(4-Aminomethyl-piperidin-4-ylmethyl)-methanesulfonamide;

50 (4-Aminomethyl-piperidin-4-ylmethyl)-phosphonic acid;

55 2-(4-Aminomethyl-piperidin-4-yl)-N-hydroxy-acetamide;

60 3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

65 3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

70 C-[4-(1H-Tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;

75 N-(4-Aminomethyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

80 3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

85 C-[4-(2-Oxo-2,3-dihydro-2 λ^4 -[1,2,3,5]oxathiadiazol-4-ylmethyl)-piperidin-4-yl]-methylamine;

90 (4-Aminomethyl-piperidin-4-yl)-methanesulfonamide;

95 (4-Aminomethyl-piperidin-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-piperidin-4-ylmethyl)-acetamide;
N-(4-Aminomethyl-piperidin-4-ylmethyl)-2-phenyl-acetamide;
N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-methanesulfonamide;
(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-phosphonic acid;
5 2-(4-Aminomethyl-1-methyl-piperidin-4-yl)-N-hydroxy-acetamide;
3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-
one;
3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-
5-thione;
10 C-[1-Methyl-4-(1H-tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;
N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-
methanesulfonamide;
3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-
5-one;
15 C-[1-Methyl-4-(2-oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-
ylmethyl)-piperidin-4-yl]-methylamine;
(4-Aminomethyl-1-methyl-piperidin-4-yl)-methanesulfonamide;
(4-Aminomethyl-1-methyl-piperidin-4-yl)-methanesulfonic acid;
N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-acetamide;
20 N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-2-phenyl-acetamide;
N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-methanesulfonamide;
(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-phosphonic acid;
2-(4-Aminomethyl-1-benzyl-piperidin-4-yl)-N-hydroxy-acetamide;
3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-
25 one;
3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-
5-thione;
C-[1-Benzyl-4-(1H-tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;
N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-
30 methanesulfonamide;
3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-
one;

C-[1-Benzyl-4-(2-oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-piperidin-4-yl]-methylamine;

(4-Aminomethyl-1-benzyl-piperidin-4-yl)-methanesulfonamide;

(4-Aminomethyl-1-benzyl-piperidin-4-yl)-methanesulfonic acid;

5 N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-acetamide; and

N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-2-phenyl-acetamide.

Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, 10 maleic, succinic, methanesulfonic acid, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, or calcium are formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The carboxyl group of the amino acids can be 15 esterified by known means.

The terms used to define the invention are as described below.

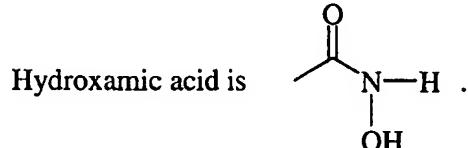
Sulfonamides are those of formula -NHSO₂R₁₅ or -SO₂NHR₁₅ wherein

R₁₅ is a straight or branched alkyl group of from 1 to 6 carbons or a trifluoromethyl.

20 Amides are compounds of formula -NHCOR₁₂ wherein R₁₂ is straight or branched alkyl of from 1 to 6 carbons, benzyl, and phenyl.

Phosphonic acids are -PO₃H₂.

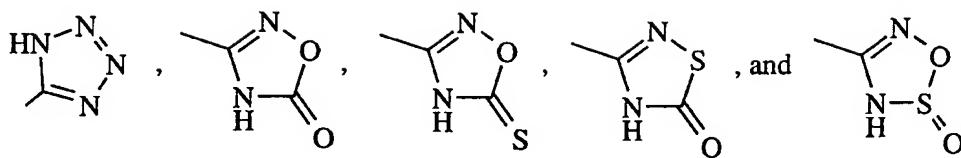
Sulfonic acids are -SO₃H .



25 Heterocycles are groups of from 1 to 2 rings, with from 1 to 6 heteroatoms selected from oxygen, nitrogen, and sulfur.

Preferred heterocycles are

-9-



5 The term alkyl is a straight or branched group of from 1 to 11 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, 2-butyl, tert-butyl, pentyl, hexyl, and n-hexyl, heptyl, octyl, nonyl, decyl, and undecyl except as where otherwise stated.

The cycloalkyl groups are from 3 to 8 carbons and are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl unless otherwise stated.

10 The benzyl and phenyl groups may be unsubstituted or substituted by from 1 to 3 substituents selected from hydroxy, carboxy, carboalkoxy, halogen, CF₃, nitro, alkyl, and alkoxy. Preferred are halogens.

Alkoxy is as defined above for alkyl.

Halogen is fluorine, chlorine, and bromine and preferred are fluorine and chlorine.

15 Carboalkoxy is -COOalkyl wherein alkyl is as described above. Preferred are carbomethoxy and carboethoxy.

20 Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

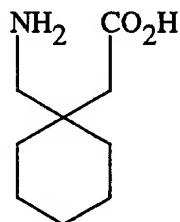
25 The radioligand binding assay using [³H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue was used ("The Novel Anti-convulsant Drug, Gabapentin, Binds to the $\alpha_2\delta$ Subunit of a Calcium Channel", Gee N.S., et al., *J. Biol Chem*, 1996;271(10):5768-5776).

-10-

The compounds of the invention will show good binding affinity to the $\alpha_2\delta$ subunit. Gabapentin (Neurontin®) is about 0.10 to 0.12 μM in this assay.

Since the compounds of the instant invention will also bind to the subunit, they are expected to exhibit pharmacologic properties comparable to gabapentin. For example, as agents for convulsions, anxiety, and pain.

The compounds of the invention are related to Neurontin®, a marketed drug effective in the treatment of epilepsy. Neurontin® is 1-(aminomethyl)-cyclohexaneacetic acid of structural formula



10 The compounds of the invention are also expected to be useful in the treatment of epilepsy.

The present invention also relates to therapeutic use of the compounds of the mimetic as agents for neurodegenerative disorders.

15 Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and epilepsy.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

20 Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke.

Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia such as in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

25 Pain refers to acute as well as chronic pain.

-11-

Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia.

Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive.

5 Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, 10 uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache.

15 Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

20 Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, and hypotension as well as similar injuries seen during procedures from embolism, hyperfusion, and hypoxia.

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

25 A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

30 The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood.

These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood 5 alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 10 1994.

GABA is an inhibitory neurotransmitter with the central nervous system. Within the general context of inhibition, it seems likely that GABA-mimetics might decrease or inhibit cerebral function and might therefore slow function and decrease mood leading to depression.

15 The compounds of the instant invention may produce an anticonvulsant effect through the increase of newly created GABA at the synaptic junction. If gabapentin does indeed increase GABA levels or the effectiveness of GABA at the synaptic junction, then it could be classified as a GABA-mimetic and might decrease or inhibit cerebral function and might, therefore, slow function and 20 decrease mood leading to depression.

The compounds of the invention will be useful in the treatment of gastrointestinal disorders, especially irritable bowel syndrome (IBS).

25 The fact that a GABA agonist or GABA-mimetic might work just the opposite way by increasing mood and thus, be an antidepressant, is a new concept, different from the prevailing opinion of GABA activity heretofore.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

MATERIAL AND METHODS

Carrageenin-Induced Hyperalgesia

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesymeter (Randall-Sellitto Method: Randall L.O., Sellitto J.J., 5 A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn., 4:409-419 (1957)). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent 10 any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 μ L of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 hours after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin (3-300 mg/kg, s.c.), 15 morphine (3 mg/kg, s.c.), or saline at 3.5 hours after carrageenin and nociceptive thresholds were examined at 4, 4.5, and 5 hours post carrageenin.

Semicarbazide-Induced Tonic Seizures

Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is 20 noted. Any mice not convulsing within 2.0 hours after semicarbazide are considered protected and given a maximum latency score of 120 minutes.

Animals

Male Hooded Lister rats (200-250 g) are obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) are obtained from Bantin and 25 Kingman (Hull, UK). Both rodent species are housed in groups of six. Ten Common Marmosets (*Callithrix Jacchus*) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) are housed in pairs. All animals are housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Drug Administration

Drugs are administered either intraperitoneally (IP) or subcutaneously (SC) 40 minutes before the test in a volume of 1 mL/kg for rats and marmosets and 10 mL/kg for mice.

5 Mouse Light/Dark Box

The apparatus is an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) and a large (3/5) area by a partition that extended 20 cm above the walls (Costall B., et al., Exploration of mice in a black and white box: validation as a model of anxiety. Pharmacol. Biochem. Behav., 32:777-785 (1989)).

10 There is a 7.5 x 7.5 cm opening in the center of the partition at floor level. The small compartment is painted black and the large compartment white. The white compartment is illuminated by a 60-W tungsten bulb. The laboratory is illuminated by red light. Each mouse is tested by placing it in the center of the 15 white area and allowing it to explore the novel environment for 5 minutes. The time spent in the illuminated side is measured (Kilfoil T., et al., Effects of anxiolytic and anxiogenic drugs on exploratory activity in a simple model of anxiety in mice. Neuropharmacol., 28:901-905 (1989)).

15 Rat Elevated X-Maze

20 A standard elevated X-maze (Handley S.L., et al., Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behavior. Naunyn-Schiedeberg's Arch. Pharmacol., 327:1-5 (1984)), was automated as previously described (Field, et al., Automation of the rat elevated X-maze test of anxiety. Br. J. Pharmacol., 102(Suppl):304P (1991)). The 25 animals are placed on the center of the X-maze facing one of the open arms. For determining anxiolytic effects the entries and time spent on the end half sections of the open arms is measured during the 5-minute test period (Costall, et al., Use of the elevated plus maze to assess anxiolytic potential in the rat. Br. J. Pharmacol., 96(Suppl):312P (1989)).

Marmoset Human Threat Test

5 The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) is recorded during the 2-minute test period. The body postures scored are slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal is exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores is analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments are carried 10 out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound is 40 minutes.

Rat Conflict Test

15 Rats are trained to press levers for food reward in operant chambers. The schedule consists of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signaled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signaled by chamber lights off. The degree of footshock is adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats receive saline vehicle on training days.

20 The compounds of the instant invention are also expected to be useful in the treatment of pain and phobic disorders (Am. J. Pain Manag., 5:7-9 (1995)).

25 The compounds of the instant invention are also expected to be useful in treating the symptoms of manic, acute or chronic, single upside, or recurring depression. They are also expected to be useful in treating and/or preventing bipolar disorder (United States Patent Number 5,510,381).

TNBS-Induced Chronic Visceral Allodynia In Rats

30 Injections of trinitrobenzene sulfonic (TNBS) into the colon have been found to induce chronic colitis. In human, digestive disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. Consequently, this study was designed to

evaluate the effect of injection of TNBS into the colon on visceral pain threshold in a experimental model of colonic distension.

Animals and Surgery

Male Sprague-Dawley rats (Janvier, Le Genest-St-Ilse, France) weighing 340-400 g are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 am to 8:00 pm). Under anesthesia (ketamine 80 mg/kg i.p; acepromazin 12 mg/kg ip), the injection of TNBS (50 mg/kg) or saline (1.5 mL/kg) is performed into the proximal colon (1 cm from the cecum). After the surgery, animals are individually housed in polypropylene cages and kept in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 am to 8:00 pm) during 7 days.

Experimental Procedure

At Day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. The balloon is progressively inflated by step of 5 mm Hg, from 0 to 75 mm Hg, each step of inflation lasting 30 seconds. Each cycle of colonic distension is controlled by a standard barostat (ABS, St-Dié, France). The threshold corresponds to the pressure which produced the first abdominal contraction and the cycle of distension is then discontinued. The colonic threshold (pressure expressed in mm Hg) is determined after performance of four cycles of distension on the same animal.

Determination of the Activity of the Compound

Data is analyzed by comparing test compound-treated group with TNBS-treated group and control group. Mean and sem are calculated for each group. The antiallodynic activity of the compound is calculated as follows:

$$\text{Activity (\%)} = (\text{group C} - \text{group T}) / (\text{group A} - \text{group T})$$

Group C: mean of the colonic threshold in the control group

Group T: mean of the colonic threshold in the TNBS-treated group

Group A: mean of the colonic threshold in the test compound-treated

30 group

Statistical Analysis

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

5 Compounds

TNBS is dissolved in EtOH 30% and injected under a volume of 0.5 mL/rat. TNBS is purchased from Fluka.

Oral administration of the test compound or its vehicle is performed 1 hour before the colonic distension cycle.

10 Sub-cutaneous administration of the test compound or its vehicle is performed 30 minutes before the colonic distension cycle.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, 15 intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise 20 as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, 25 suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

30 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, 5 cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges 10 can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to 15 solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

20 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

25 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. 30 Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as 5 packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

10 The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

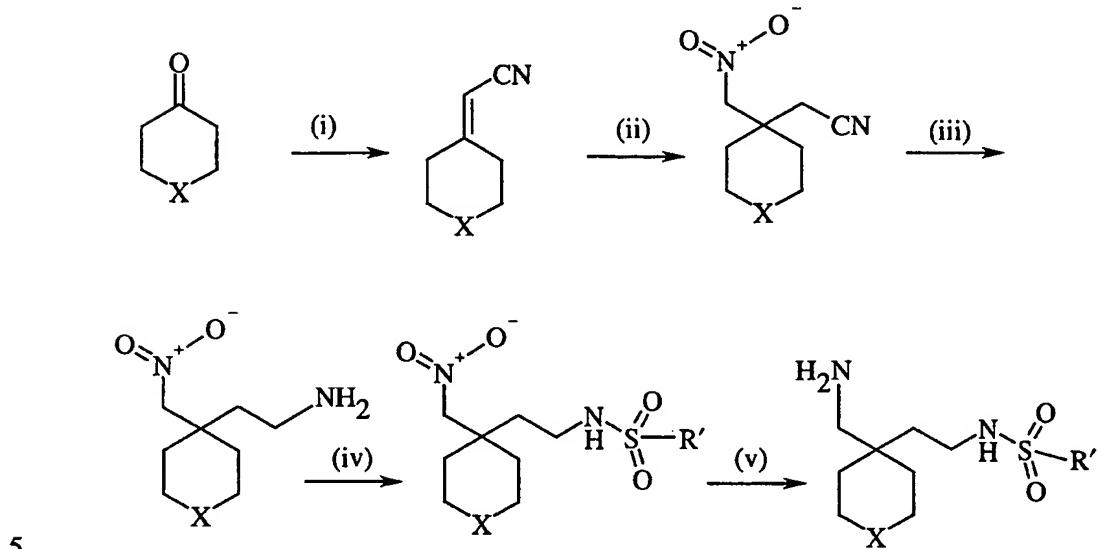
15 In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within 20 the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

In the following schemes, the X can be in the 3 or 4 position.

Sulfonamides can be synthesized by the route outlined in Scheme 1

wherein X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph.

Scheme 1

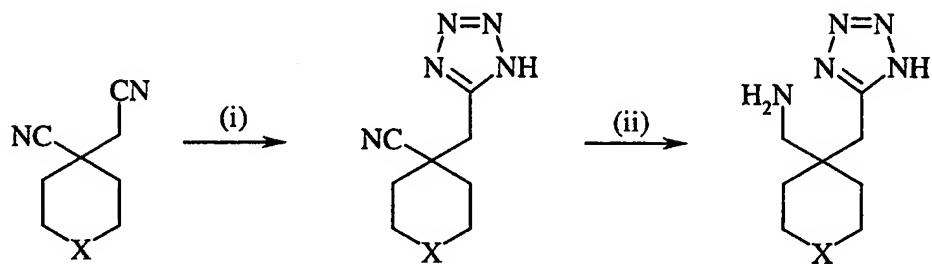


Reagents:

- (i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;
- (ii) MeNO₂, tetrabutylammonium fluoride, tetrahydrofuran;
- (iii) Borane methylsulphide, toluene;
- 10 (iv) NEt₃, R'SO₂Cl, tetrahydrofuran; and
- (v) Fe/HCl.

Tetrazoles can be synthesized by the route outlined in Scheme 2 wherein X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph.

Scheme 2



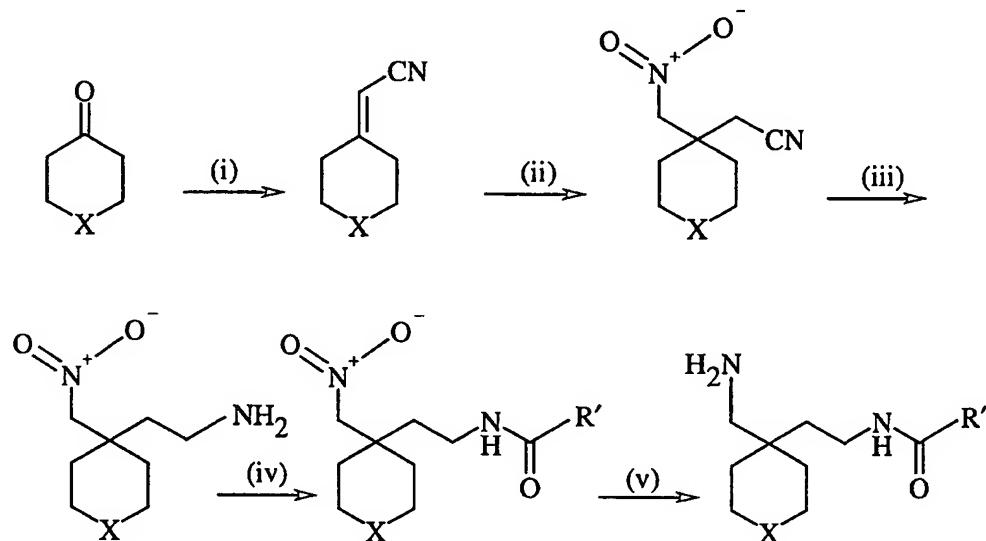
5 Reagents:

- (i) Trimethylsilylazide, Trimethylaluminium (2M in hexanes), toluene;
- (ii) Fe/HCl.

-22-

Amides where R' is Me, CH₂Ph, CF₃ can be synthesized by the route outlined in Scheme 3.

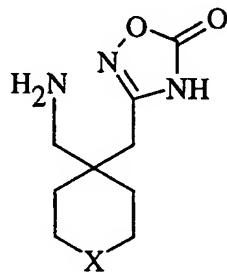
Scheme 3



5 Reagents:

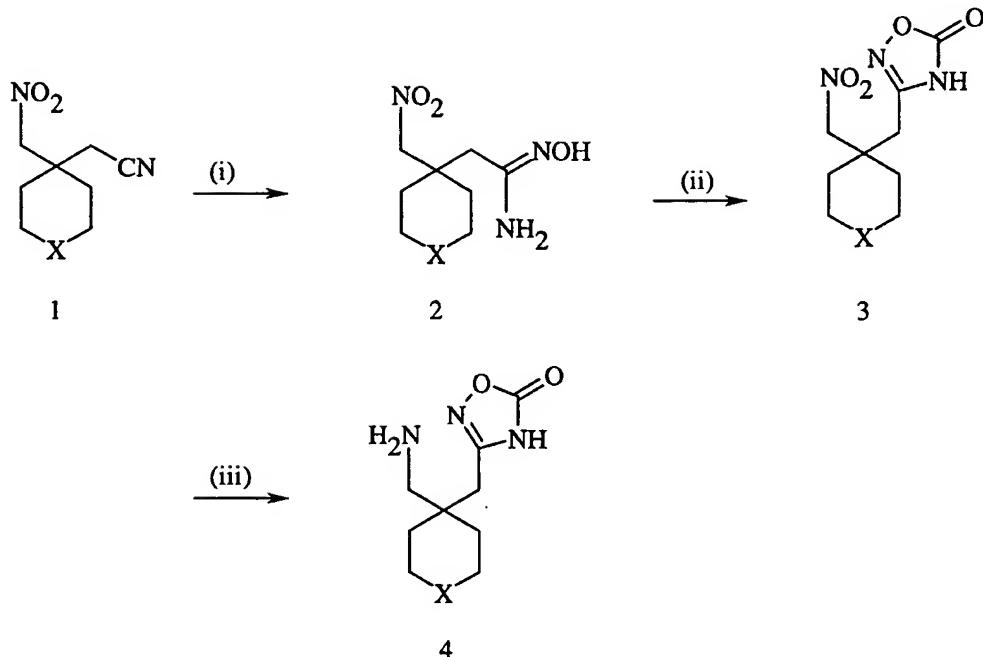
- (i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;
- (ii) MeNO₂, tetrabutylammonium fluoride, tetrahydrofuran;
- (iii) Borane methylsulphide, toluene;
- (iv) NEt₃, R'COCl, tetrahydrofuran;
- 10 (v) Fe/HCl.

Heterocycles such as



where X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph can be synthesized by the route outlined in Scheme 4.

Scheme 4



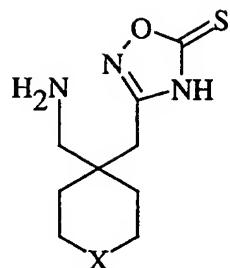
(i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Et_3N ;
 (ii) iBuOCOCl , pyridine followed by reflux in xylene;
 5 (iii) Fe/HCl .

Compound 1 can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

The heterocyclic compound 3 can be prepared from compound 2 by treatment with iso-butyl chloroformate in the presence of a base such as pyridine followed by reflux in a solvent such as xylene.

The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

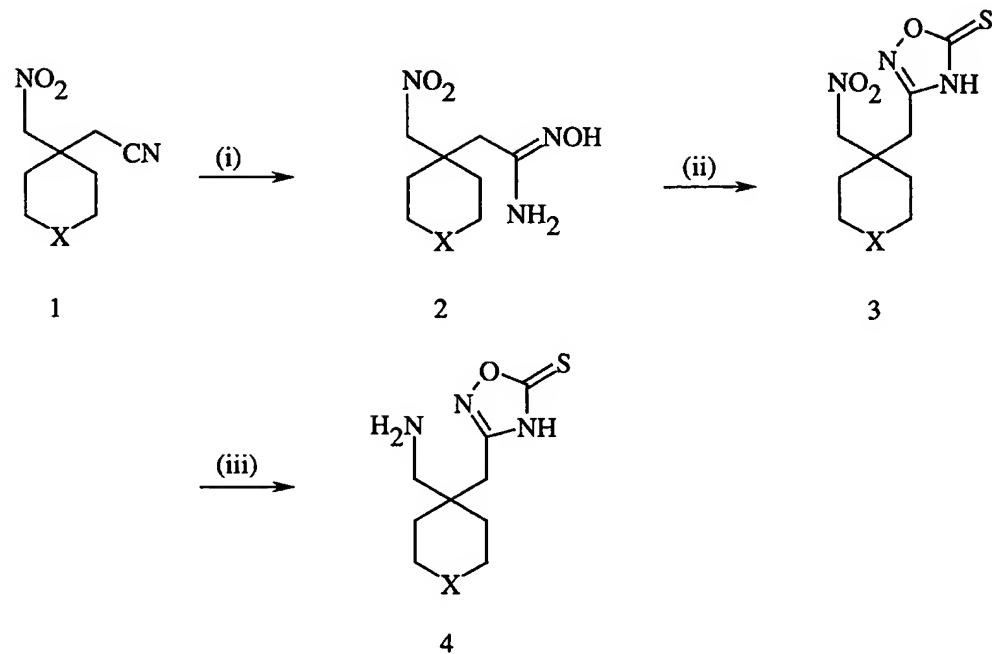
Heterocycles such as



where X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph can be synthesized by the route shown in Scheme 5.

5

Scheme 5



(i) NH₂OH·HCl, Et₃N;

(ii) 1,1'-thiocarbonyldiimidazole followed by DBU or DBN;

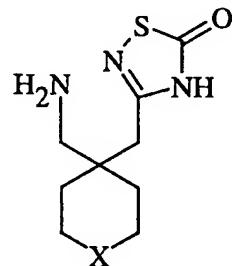
(iii) Fe/HCl.

Compound 1 [(1-Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

5 The heterocyclic compound 3 can be prepared from compound 2 by treatment with 1,1'-thiocarbonyldiimidazole followed by a base such as 1,8-diazabicyclo-[4.5.0]-undec-7-ene.

The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

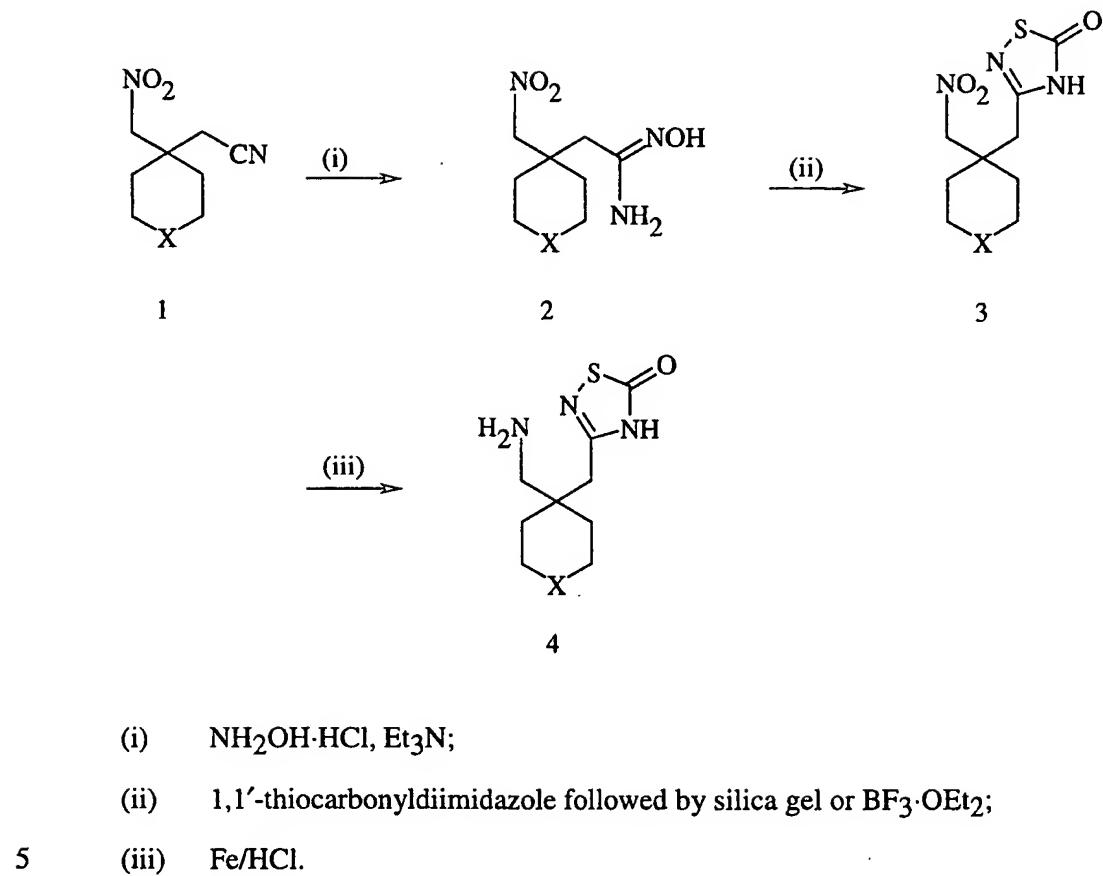
Heterocycles such as



10

where X is O, S, SO, SO₂, NH, NMe, NCH₂Ph can be synthesized following the route shown in Scheme 6.

Scheme 6

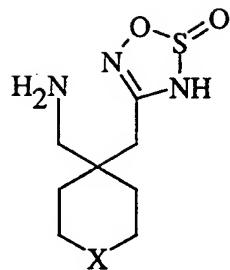


Compound 1 [(1-Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

The heterocyclic compound 3 can be prepared from compound 2 by treatment with 1,1'-thiocarbonyldiimidazole followed by treatment with silica gel or boron trifluoride etherate.

The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

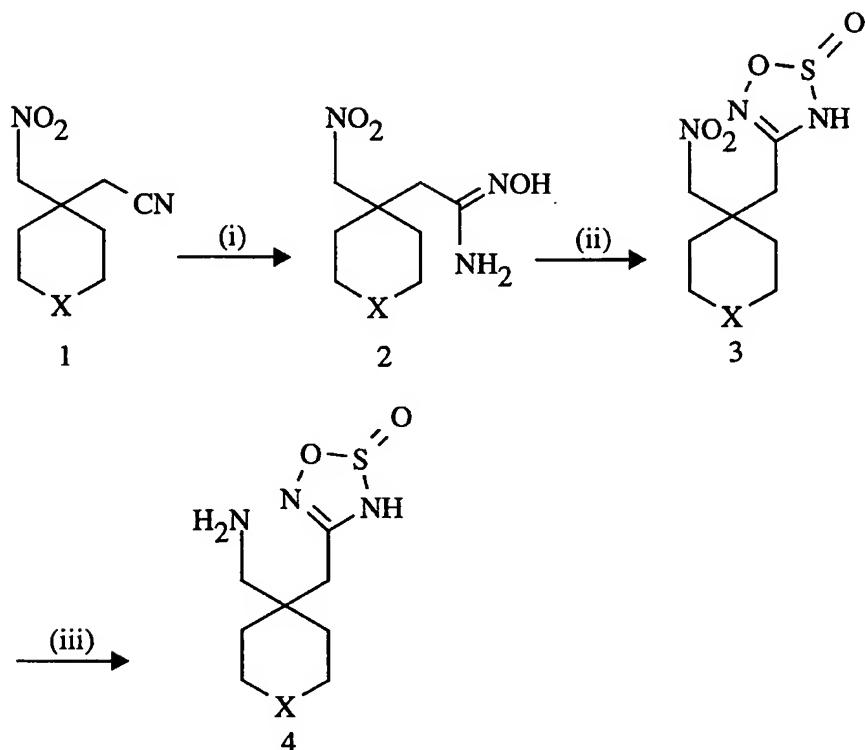
Heterocycles such as



where X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph can be synthesized following the route outlined in Scheme 7.

5

Scheme 7



(i) NH₂OH·HCl, Et₃N;

(ii) Pyridine, SOCl₂;

(iii) Fe/HCl.

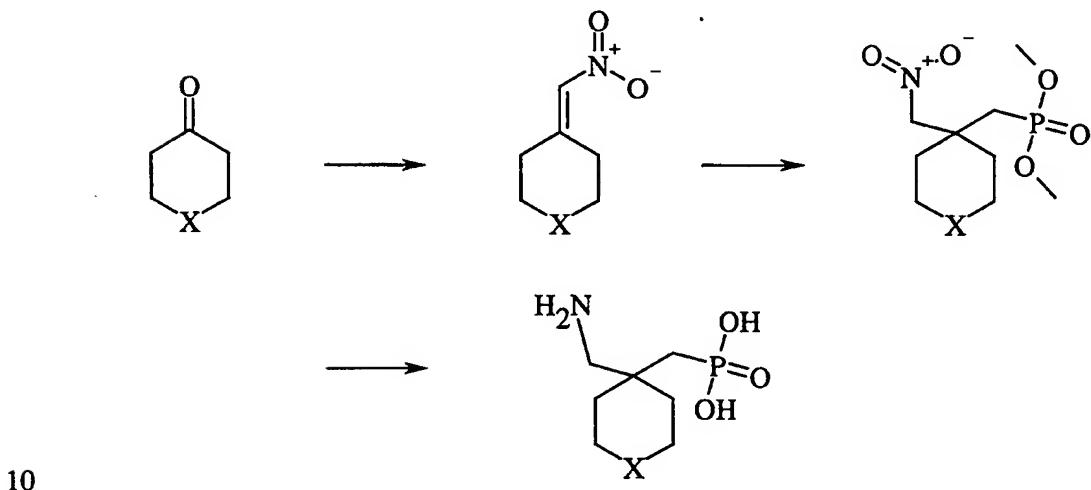
Compound 1 [(1-Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

5 The heterocyclic compound 3 can be prepared from compound 2 by treatment with thionyl chloride in the presence of a base such as pyridine.

The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

Synthesis of phosphonate is found in Scheme 8.

Scheme 8

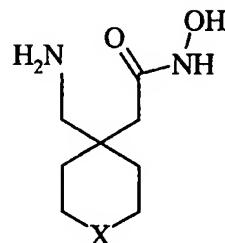


Reagents:

- (i) MeNO₂;
- (ii) Dimethyl lithiummethylphosphonate, THF;
- (iii) Fe/HCl.

15 The phosphonate where X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph can be synthesized by treatment of the ketone with nitromethane and a suitable base such as butyl lithium, followed by treatment of the nitroalkene with dimethyl lithiummethylphosphonate in a suitable solvent such as tetrahydrofuran and then deprotection and reduction with iron in hydrochloric acid.

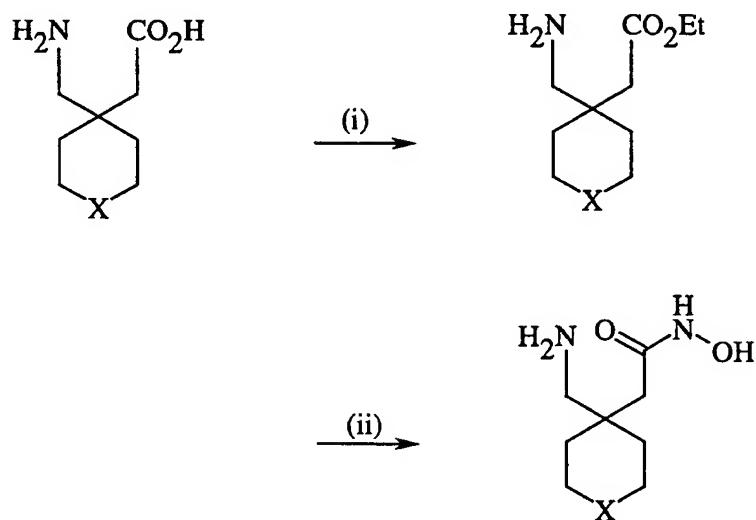
Synthesis of hydroxamic acids of formula



can be synthesized by the route outlined in Scheme 9 where X is O, S, SO, SO₂, NH, NMe, or NCH₂Ph.

5

Scheme 9



Reagents:

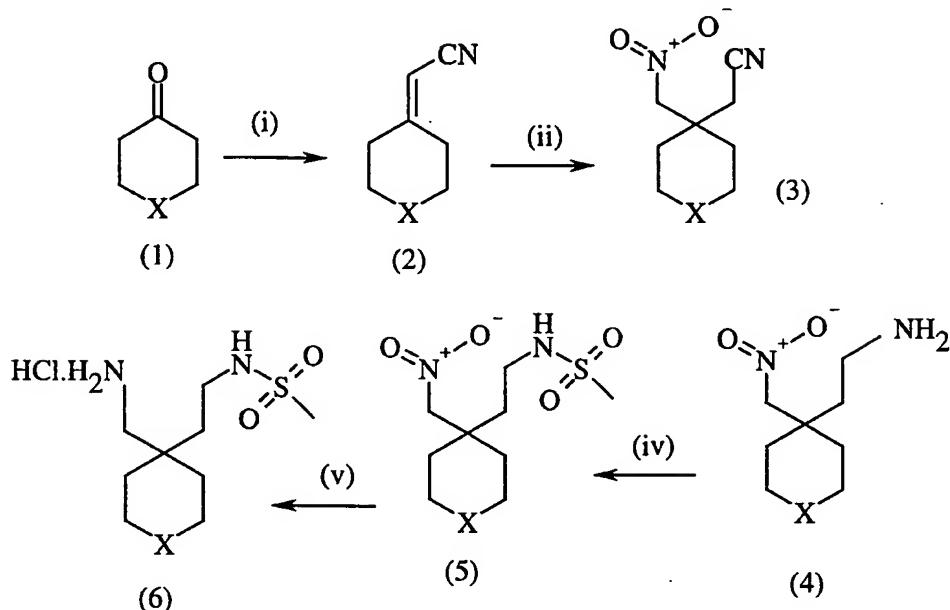
- (i) Ethanol/HCl;
- (ii) H₂NOH, NaOH.

10

The hydroxamic acids can be synthesized from the amino acid by treatment with ethanol and HCl followed by treatment with hydroxylamine hydrochloride and a base such as sodium hydroxide in a suitable solvent such as methanol.

The following examples are illustrative of the instant invention; they are not intended to limit the scope.

EXAMPLE 1



5

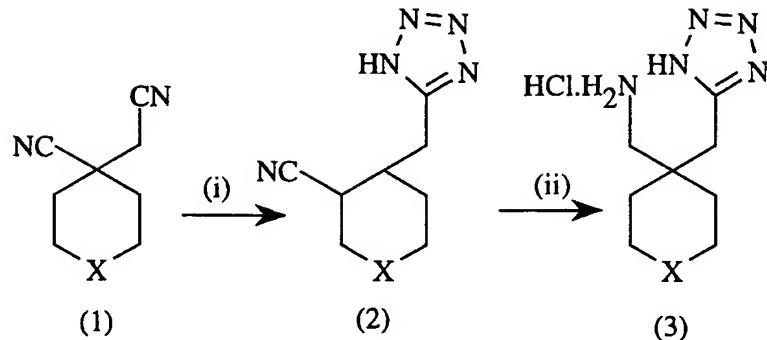
In this example, X is at the 3 or 4 position and can be, for example, O, S, or NCH_3 .

Reagents:

- (i) Diethylcyanomethyl phosphonate, NaH , tetrahydrofuran;
- (ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;
- 10 (iii) Borane methyl sulphide, toluene;
- (iv) Triethylamine, methanesulphonyl chloride, tetrahydrofuran;
- (v) 10% Pd-C , hydrogen gas, methanol then HCl .

-31-

EXAMPLE 2

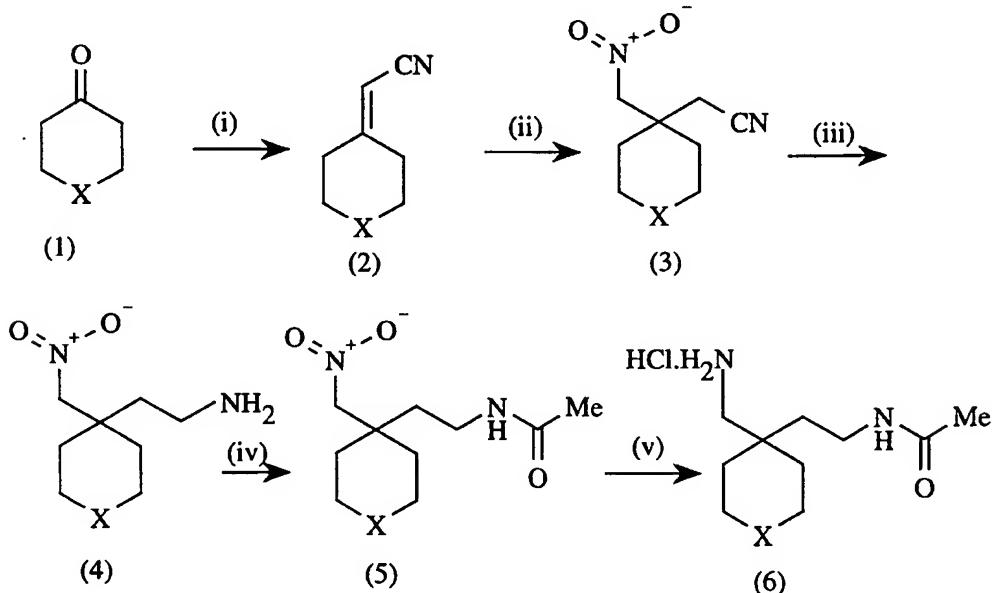


In this example, X is for example, at the 3 or 4 position and is O, S, or NCH_3 .

5 Reagents:

- (i) Trimethylsilylazide, trimethylaluminium (2 M in hexanes), toluene;
- (ii) Raney Nickel, hydrogen gas, methanol then HCl.

EXAMPLE 3



10

In this example, X can be at the 3 or 4 position and is O, S, or NCH_3 .

Reagents:

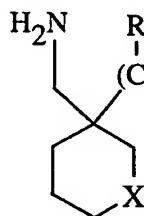
- (i) Diethylcyanomethyl phosphonate, NaH , tetrahydrofuran;

-32-

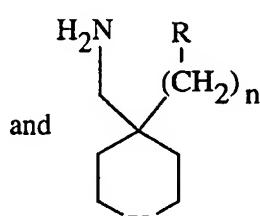
- (ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;
- (iii) Borane methyl sulphide, toluene;
- (iv) Triethylamine, acetyl chloride, tetrahydrofuran;
- (v) 10% Pd-C, hydrogen gas, methanol then HCl

CLAIMS

1. The compounds of the invention are those of formula



1D



1E

or a pharmaceutically acceptable salt thereof wherein:

5 n is an integer of from 0 to 2:

R is sulfonamide

amide

phosphonic acid.

heterocycle.

10 sulfonic acid, or

hydroxamic acid; and

X is -O-, -S-, -S(O)-, -S(O)2-, or NR'1 wherein R'1 is hydrogen, straight or

branched alkyl of from 1 to 6 carbons, benzyl, $-\text{C}(\text{O})\text{R}'_2$ wherein

R' is straight or branched alkyl of 1 to 6 carbons, benzyl or phenyl

15 or CO_2R' 's wherein R's is straight or branched alkyl of from 1 to

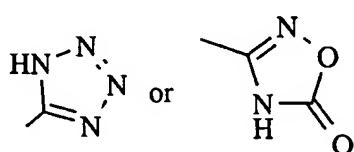
6 carbons, or benzyl when in the benzyl carbonyl group, can be

unsubstituted or substituted by from 1 to 3 substituents selected

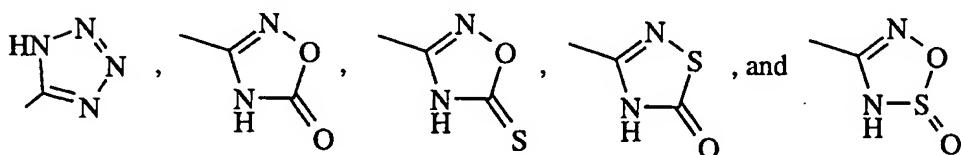
from halogen, trifluoromethyl, and nitro

2. A compound according to Claim 1 wherein n is 1 and R is

20



3. A compound according to Claim 1 wherein R is a sulfonamide selected from $-\text{NHSO}_2\text{R}_{15}$ or $-\text{SO}_2\text{NHR}_{15}$ wherein R_{15} is straight or branched alkyl or trifluoromethyl.
4. A compound according to Claim 1 wherein R is a phosphonic acid, $-\text{PO}_3\text{H}_2$.
5. A compound according to Claim 1 wherein R is hydroxamic acid.
6. A compound according to Claim 1 wherein R is a heterocycle selected from



10 7. A compound according to Claim 1 wherein R is an amide of formula
-NHCOR₁₂, wherein R₁₂ is straight or branched alkyl of from 1 to
6 carbons, benzyl, or phenyl.

15 8. A compound according to Claim 1 and selected from:
N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-
methanesulfonamide;
(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-phosphonic acid
2-(4-Aminomethyl-tetrahydro-pyran-4-yl)-N-hydroxy-acetamide
3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-
[1,2,4]oxadiazol-5-one;
3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-
[1,2,4]oxadiazole-5-thione;
C-[4-(1H-Tetrazol-5-ylmethyl)-tetrahydro-pyran-4-yl]-
methylamine;

N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

3-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

5 C-[4-(2-Oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-tetrahydro-pyran-4-yl]-methylamine;

(4-Aminomethyl-tetrahydro-pyran-4-yl)-methanesulfonamide;

(4-Aminomethyl-tetrahydro-pyran-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-acetamide;

10 N-(4-Aminomethyl-tetrahydro-pyran-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-methanesulfonamide;

(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-phosphonic acid;

15 2-(4-Aminomethyl-tetrahydro-thiopyran-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

20 3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[4-(1H-Tetrazol-5-ylmethyl)-tetrahydro-thiopyran-4-yl]-methylamine;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

25 3-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[4-(2-Oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-tetrahydro-thiopyran-4-yl]-methylamine;

30 (4-Aminomethyl-tetrahydro-thiopyran-4-yl)-methanesulfonamide;

(4-Aminomethyl-tetrahydro-thiopyran-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-acetamide;

5 N-(4-Aminomethyl-tetrahydro-thiopyran-4-ylmethyl)-2-phenyl-acetamide;

 N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-methanesulfonamide;

10 (4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-phosphonic acid;

 2-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-N-hydroxy-acetamide;

15 3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

 3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

 C-[1-Oxo-4-(1H-tetrazol-5-ylmethyl)-hexahydro-1 λ ⁴-thiopyran-4-yl]-methylamine;

20 N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

 3-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

 C-[1-Oxo-4-(2-oxo-2,3-dihydro-2 λ ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-hexahydro-1 λ ⁴-thiopyran-4-yl]-methylamine;

25 4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-methanesulfonamide;

 (4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-yl)-methanesulfonic acid;

 N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-acetamide;

 N-(4-Aminomethyl-1-oxo-hexahydro-1 λ ⁴-thiopyran-4-ylmethyl)-2-phenyl-acetamide;

30 N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-ylmethyl)-methanesulfonamide;

(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-ylmethyl)-
phosphonic acid;

2-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-yl)-N-
hydroxy-acetamide;

5 3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-4H-[1,2,4]oxadiazol-5-thione;

10 C-[1,1-Dioxo-4-(1H-tetrazol-5-ylmethyl)-hexahydro-1 λ ⁶-
thiopyran-4-yl]-methylamine;

N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

3-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

15 C-[1,1-Dioxo-4-(2-oxo-2,3-dihydro-2 λ ⁴-[1,2,3,5]oxathiadiazol-4-
ylmethyl)-hexahydro-1 λ ⁶-thiopyran-4-yl]-methylamine;

(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-yl)-
methanesulfonamide;

(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-yl)-
methanesulfonic acid;

20 N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-acetamide;

N-(4-Aminomethyl-1,1-dioxo-hexahydro-1 λ ⁶-thiopyran-4-
ylmethyl)-2-phenyl-acetamide;

25 N-(4-Aminomethyl-piperidin-4-ylmethyl)-methanesulfonamide;

(4-Aminomethyl-piperidin-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-piperidin-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-
one;

3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[4-(1H-Tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;

N-(4-Aminomethyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

5 3-(4-Aminomethyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[4-(2-Oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-piperidin-4-yl]-methylamine;

10 (4-Aminomethyl-piperidin-4-yl)-methanesulfonamide;

(4-Aminomethyl-piperidin-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-piperidin-4-ylmethyl)-acetamide;

N-(4-Aminomethyl-piperidin-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-

15 methanesulfonamide;

(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-1-methyl-piperidin-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

20 3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-Methyl-4-(1H-tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;

N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

25 3-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-Methyl-4-(2-oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-piperidin-4-yl]-methylamine;

30 (4-Aminomethyl-1-methyl-piperidin-4-yl)-methanesulfonamide;

(4-Aminomethyl-1-methyl-piperidin-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-acetamide;

N-(4-Aminomethyl-1-methyl-piperidin-4-ylmethyl)-2-phenyl-acetamide;

N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-methanesulfonamide;

5 (4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-phosphonic acid;

2-(4-Aminomethyl-1-benzyl-piperidin-4-yl)-N-hydroxy-acetamide;

3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

10 3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-Benzyl-4-(1H-tetrazol-5-ylmethyl)-piperidin-4-yl]-methylamine;

N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-C,C,C-trifluoro-methanesulfonamide;

15 3-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-Benzyl-4-(2-oxo-2,3-dihydro-2λ⁴-[1,2,3,5]oxathiadiazol-4-ylmethyl)-piperidin-4-yl]-methylamine;

(4-Aminomethyl-1-benzyl-piperidin-4-yl)-methanesulfonamide;

20 (4-Aminomethyl-1-benzyl-piperidin-4-yl)-methanesulfonic acid;

N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-acetamide; and

N-(4-Aminomethyl-1-benzyl-piperidin-4-ylmethyl)-2-phenyl-acetamide.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

25

10. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

-40-

11. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
12. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
13. A method for treating depression comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
14. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
15. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
16. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
17. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
18. A method for treating gastrointestinal damage comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

-41-

19. A method for treating inflammation comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.
20. A method for treating gastrointestinal disorders, especially IBS comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

5

INTERNATIONAL SEARCH REPORT

In	nternational Application No
PCT/US 98/23991	

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 6	C07D211/26	A61K31/445	C07D211/34	C07F9/38	A61K31/66
	C07D413/06	C07D401/06	C07D417/06	C07D419/06	C07D309/04
	A61K31/35	A61K31/41	C07D407/06	C07D335/02	A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HERMANS B. ET AL.: "4-Substituted piperidines. III. Reduction of 1-benzyl-4-cyano-4-t-aminopiperidines with lithium aluminium hydride" JOURNAL OF MEDICINAL CHEMISTRY, vol. 9, no. 1, January 1966, pages 49-52, XP002096770</p> <p>see compounds 9, 12</p> <p>see page 50; table I</p> <p>---</p>	1
X	<p>EP 0 506 532 A (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE)</p> <p>30 September 1992</p> <p>see intermediates of compounds 35 and 88</p> <p>see claim 7, formula 5</p> <p>---</p> <p>-/--</p>	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

17 March 1999

Date of mailing of the international search report

12.04.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23991

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D409/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>AIRAPETYAN G.K. ET AL.: "Derivatives of isoquinoline. 30. Synthesis of 4-spirosubstituted dioxinoisoquinolines" CHEM. HETEROCYCL. COMPD. (ENGL. TRANSL.), vol. 29, no. 5, May 1993, pages 578-581, XP002096771</p> <p>see formula IX</p> <p>see page 579</p> <p>---</p>	1
X	<p>BELLEMIN R. ET AL.: "New indole derivatives as ACAT inhibitors: Synthesis and structure-activity relationships" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 2, 1996, pages 123-132, XP004040999</p> <p>see scheme 1, compound 2W</p> <p>see page 126; table II</p> <p>---</p> <p>-/-</p>	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 March 1999

Date of mailing of the international search report

12.04.99

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

INTERNATIONAL SEARCH REPORT

Int	lational Application No
PCT/US 98/23991	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KRAUS J.L.: "Isosterism and molecular modification in drug design: Tetrazole analogue of GABA: Effects on enzymes of the .gamma.-aminobutyrate system" PHARMACOLOGICAL RESEARCH COMMUNICATIONS, vol. 15, no. 2, 1983, pages 183-189, XP002096228 see the whole document ---	1-9
Y	BURGER A.: "Isosterism and bioisosterism in drug design" PROGRESS IN DRUG DESIGN, vol. 37, 1991, pages 287-371, XP002096229 see page 332 - page 338 ---	1-9
Y	KERR D.I.B. & ONG J.: "GABA agonists and antagonists" MEDICINAL RESEARCH REVIEWS, vol. 12, no. 6, 6 November 1992, pages 593-636, XP002080823 see page 620 - page 628 ---	1-9
Y	SUMAN-CHAUHAN N. ET AL.: "Characterisation of '3H!gabapentin binding to a novel site in rat brain: Homogenate binding studies" EUROPEAN JOURNAL OF PHARMACOLOGY - MOLECULAR PHARMACOLOGY SECTION, vol. 244, no. 3, 1993, pages 293-301, XP002096653 cited in the application see compounds 6, 7 see page 297; table 1 ---	1-9
Y	HOWSON W. ET AL.: "Biological activity of 3-aminopropyl (methyl) phosphinic acid, a potent and selective GABA(B) agonist with CNS activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 4, 1993, pages 515-518, XP002096230 see the whole document ---	1-9
Y	PATANI G.A. & LA VOIE E.J.: "Bioisosterism: A rational approach in drug design" CHEMICAL REVIEWS, vol. 96, no. 8, 1996, pages 3147-3176, XP000652176 see 3. Carboxylate group bioisosteres see page 3168, left-hand column - page 3170, left-hand column ---	1-9
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23991

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 29101 A (WARNER-LAMBERT COMPANY) 14 August 1997 see the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/23991

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 10-20
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23991

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 506532	A 30-09-1992	FR 2674522	A	02-10-1992
		AT 111078	T	15-09-1994
		AU 658609	B	27-04-1995
		AU 1309492	A	01-10-1992
		CA 2063170	A	27-09-1992
		CS 9200895	A	14-10-1992
		DE 69200378	D	13-10-1994
		DE 69200378	T	09-03-1995
		DK 506532	T	20-02-1995
		ES 2064149	T	16-01-1995
		HU 65489	A	28-06-1994
		IE 65366	B	18-10-1995
		IL 101248	A	05-12-1996
		JP 5097802	A	20-04-1993
		KR 9507753	B	14-07-1995
		MX 9201365	A	01-10-1992
		NO 178260	B	13-11-1995
		NZ 242078	A	26-10-1994
		OA 9573	A	31-01-1993
		SI 9210305	A	29-02-1996
		RU 2074179	C	27-02-1997
		US 5219859	A	15-06-1993
		ZA 9202163	A	27-09-1993
-----	-----	-----	-----	-----
WO 9729101	A 14-08-1997	AU 1529597	A	28-08-1997
		CA 2244708	A	14-08-1997
		CZ 9802452	A	11-11-1998
		EP 0888325	A	07-01-1999
		NO 983612	A	06-10-1998